

L5 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN
 AN 2005:1004748 CAPLUS Full-text
 DN 143:306348
 TI Preparation of pyrrolobenzodiazepinone derivatives as antitumor agents
 IN Howard, Philip Wilson; Gregson, Stephen John
 PA Spirogen Limited, UK
 SO PCT Int. Appl., 88 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005085251	A1	20050915	WO 2005-GB768	20050301
	W:				AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
	RW:				BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRAI	GB 2004-4575	A	20040301		
	GB 2004-26392	A	20041201		
OS	MARPAT 143:306348				
GI					

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I [R1 = labile leaving group, alkenyl or substituted phenyl; R2 and R5 independently = H, OH, SH, etc.; R3 and R4 independently = H, NH2, halo, etc. or the compound is a dimer with each monomer being of formula I, where the R3 and R4 groups of each monomer form together a dimer bridge -X-R-X-; R = alkylene group, which may be interrupted by heteroatoms or aromatic rings; X = O, S or NH; R6 = carbamate-based N-protecting group; R7 = oxygen protecting group or OH or R6 and R7 together form double bond between N10 and C11] and their pharmaceutically acceptable salts, are prepared and disclosed as antitumor agents. Thus, e.g., II was prepared by palladium catalyzed coupling of III (preparation given) with trans-propenylboronic acid followed by deprotection. The in vitro cytotoxicity of I towards K562 human chronic myeloid leukemia cells was evaluated using ELISA assay and it was revealed that selected compds. of the invention displayed IC50 values of less than 1 µM. I should prove useful in the treatment of proliferative diseases such as leukemia. Pharmaceutical compns. comprising I are disclosed.

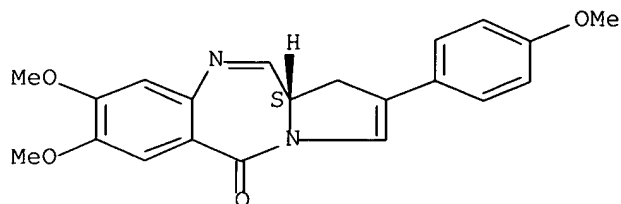
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 864754-98-3P 864754-99-4P 864755-00-0P
 864755-01-1P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (preparation of pyrrolobenzodiazepinone derivs. as antitumor agents)

RN 260544-29-4 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,11a-dihydro-7,8-dimethoxy-2-(4-methoxyphenyl)-, (11aS)- (9CI) (CA INDEX NAME)

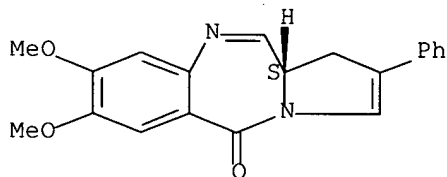
Absolute stereochemistry.



RN 260544-30-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,11a-dihydro-7,8-dimethoxy-2-phenyl-, (11aS)- (9CI) (CA INDEX NAME)

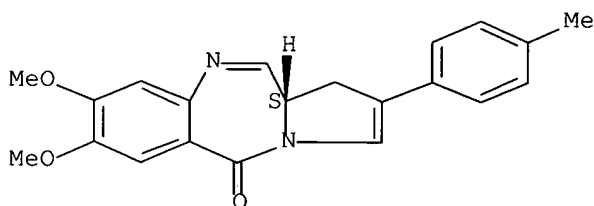
Absolute stereochemistry.



RN 489475-06-1 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,11a-dihydro-7,8-dimethoxy-2-(4-methylphenyl)-, (11aS)- (9CI) (CA INDEX NAME)

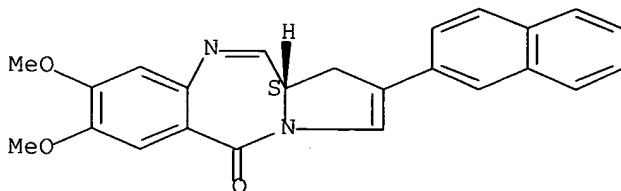
Absolute stereochemistry.



RN 692760-70-6 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,11a-dihydro-7,8-dimethoxy-2-(2-naphthalenyl)-, (11aS)- (9CI) (CA INDEX NAME)

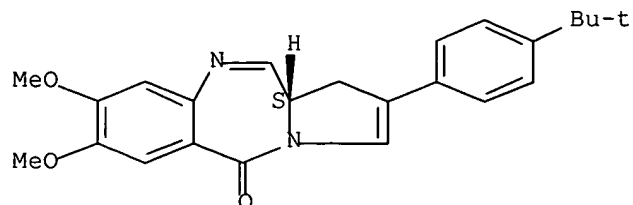
Absolute stereochemistry.



RN 692760-72-8 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 2-[4-(1,1-dimethylethyl)phenyl]-1,11a-dihydro-7,8-dimethoxy-, (11aS)- (9CI) (CA INDEX NAME)

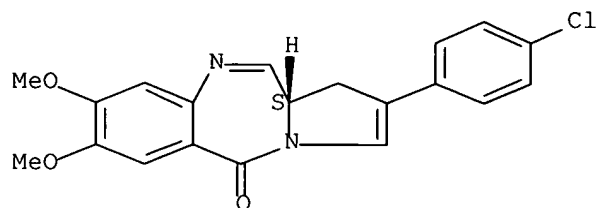
Absolute stereochemistry.



RN 692760-74-0 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 2-(4-chlorophenyl)-1,11a-dihydro-7,8-dimethoxy-, (11aS)- (9CI) (CA INDEX NAME)

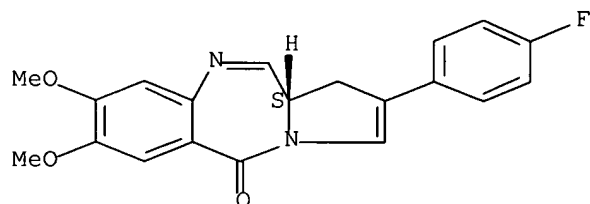
Absolute stereochemistry.



RN 692760-76-2 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 2-(4-fluorophenyl)-1,11a-dihydro-7,8-dimethoxy-, (11aS)- (9CI) (CA INDEX NAME)

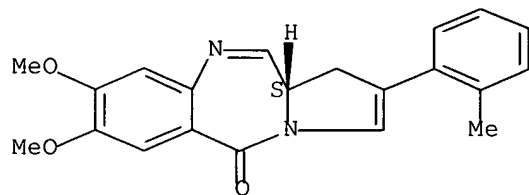
Absolute stereochemistry.



RN 692760-78-4 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,11a-dihydro-7,8-dimethoxy-2-(2-methylphenyl)-, (11aS)- (9CI) (CA INDEX NAME)

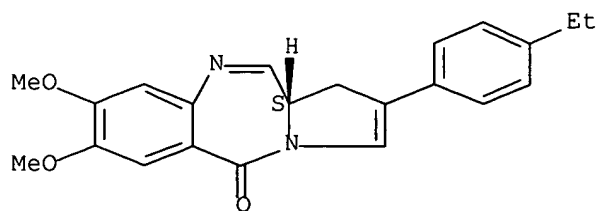
Absolute stereochemistry.



RN 692760-80-8 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 2-(4-ethylphenyl)-1,11a-dihydro-7,8-dimethoxy-, (11aS)- (9CI) (CA INDEX NAME)

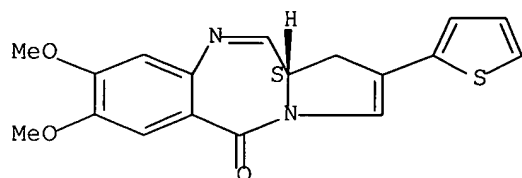
Absolute stereochemistry.



RN 692760-82-0 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,11a-dihydro-7,8-dimethoxy-2-(2-thienyl)-, (11aS)- (9CI) (CA INDEX NAME)

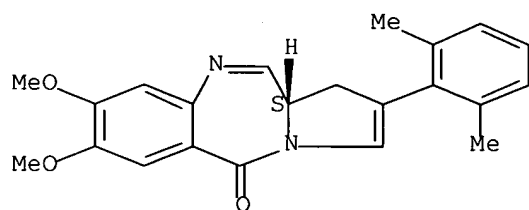
Absolute stereochemistry.



RN 692760-86-4 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 2-(2,6-dimethylphenyl)-1,11a-dihydro-7,8-dimethoxy-, (11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

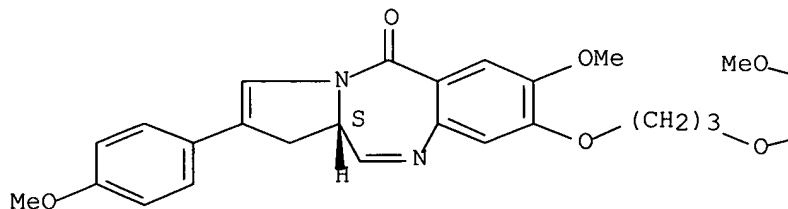


RN 864754-68-7 CAPLUS

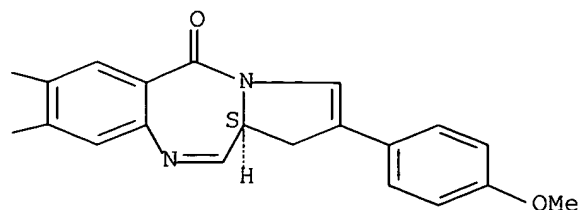
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,11a-dihydro-7-methoxy-2-(4-methoxyphenyl)-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

PAGE 1-A



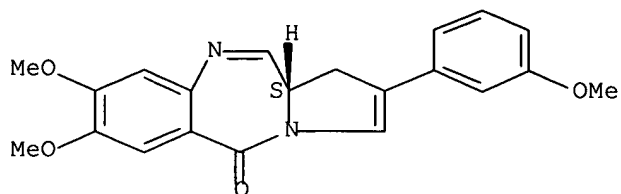
PAGE 1-B



RN 864754-77-8 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,11a-dihydro-7,8-dimethoxy-2-(3-methoxyphenyl)-, (11aS)- (9CI) (CA INDEX NAME)

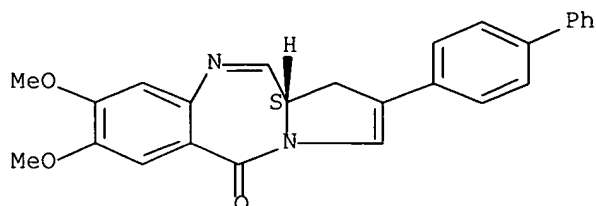
Absolute stereochemistry. Rotation (+).



RN 864754-78-9 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 2-[1,1'-biphenyl]-4-yl-1,11a-dihydro-7,8-dimethoxy-, (11aS)- (9CI) (CA INDEX NAME)

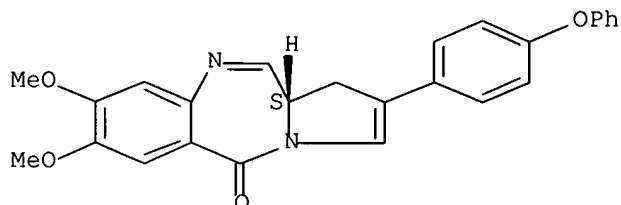
Absolute stereochemistry. Rotation (+).



RN 864754-79-0 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,11a-dihydro-7,8-dimethoxy-2-(4-phenoxyphenyl)-, (11aS)- (9CI) (CA INDEX NAME)

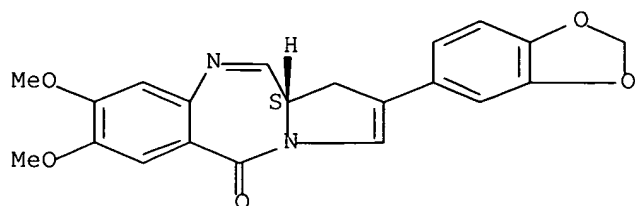
Absolute stereochemistry. Rotation (+).



RN 864754-80-3 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 2-(1,3-benzodioxol-5-yl)-1,11a-dihydro-7,8-dimethoxy-, (11aS)- (9CI) (CA INDEX NAME)

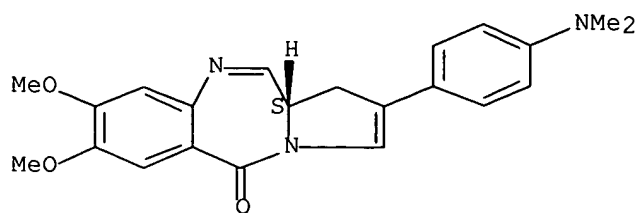
Absolute stereochemistry. Rotation (+).



RN 864754-82-5 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 2-[4-(dimethylamino)phenyl]-1,11a-dihydro-7,8-dimethoxy-, (11aS)- (9CI) (CA INDEX NAME)

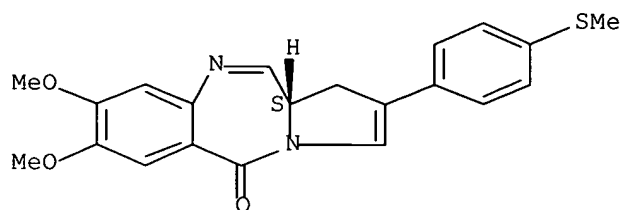
Absolute stereochemistry. Rotation (+).



RN 864754-83-6 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,11a-dihydro-7,8-dimethoxy-2-[4-(methylthio)phenyl]-, (11aS)- (9CI) (CA INDEX NAME)

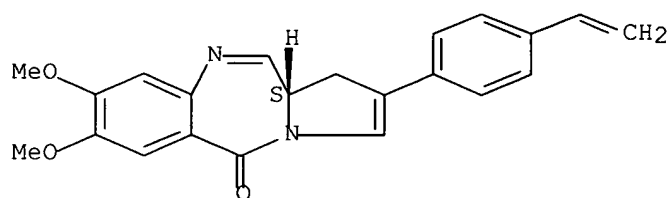
Absolute stereochemistry. Rotation (+).



RN 864754-84-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 2-(4-ethenylphenyl)-1,11a-dihydro-7,8-dimethoxy-, (11aS)- (9CI) (CA INDEX NAME)

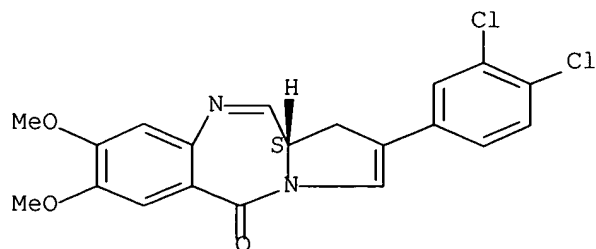
Absolute stereochemistry. Rotation (+).



RN 864754-85-8 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 2-(3,4-dichlorophenyl)-1,11a-dihydro-7,8-dimethoxy-, (11aS)- (9CI) (CA INDEX NAME)

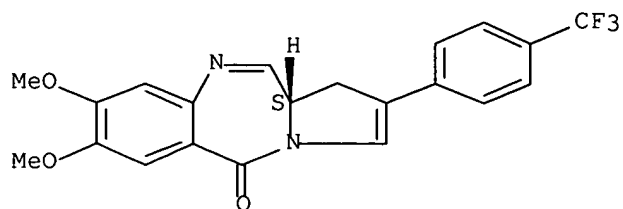
Absolute stereochemistry. Rotation (+).



RN 864754-86-9 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,11a-dihydro-7,8-dimethoxy-2-[4-(trifluoromethyl)phenyl]-, (11aS)- (9CI) (CA INDEX NAME)

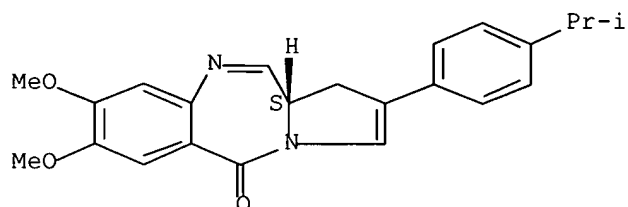
Absolute stereochemistry. Rotation (+).



RN 864754-87-0 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,11a-dihydro-7,8-dimethoxy-2-[4-(1-methylethyl)phenyl]-, (11aS)- (9CI) (CA INDEX NAME)

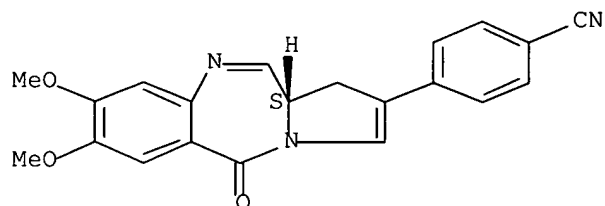
Absolute stereochemistry. Rotation (+).



RN 864754-88-1 CAPLUS

CN Benzonitrile, 4-[(11aS)-5,11a-dihydro-7,8-dimethoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-yl]- (9CI) (CA INDEX NAME)

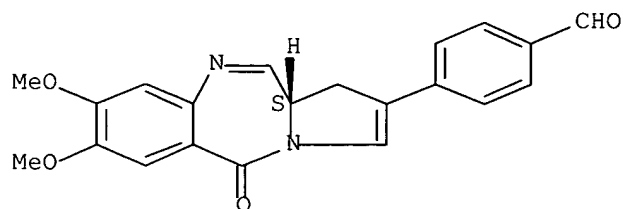
Absolute stereochemistry. Rotation (+).



RN 864754-91-6 CAPLUS

CN Benzaldehyde, 4-[(11aS)-5,11a-dihydro-7,8-dimethoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-yl]- (9CI) (CA INDEX NAME)

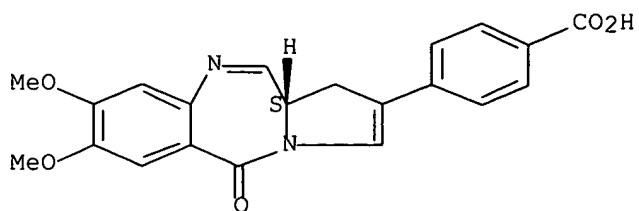
Absolute stereochemistry. Rotation (+).



RN 864754-92-7 CAPLUS

CN Benzoic acid, 4-[(11aS)-5,11a-dihydro-7,8-dimethoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-yl]- (9CI) (CA INDEX NAME)

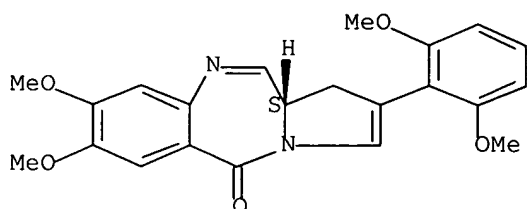
Absolute stereochemistry.



RN 864754-93-8 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 2-(2,6-dimethoxyphenyl)-1,11a-dihydro-7,8-dimethoxy-, (11aS)- (9CI) (CA INDEX NAME)

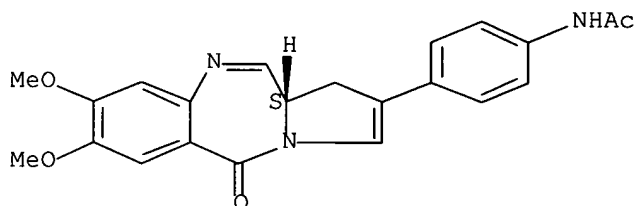
Absolute stereochemistry.



RN 864754-94-9 CAPLUS

CN Acetamide, N-[4-[(11aS)-5,11a-dihydro-7,8-dimethoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2-yl]phenyl]- (9CI) (CA INDEX NAME)

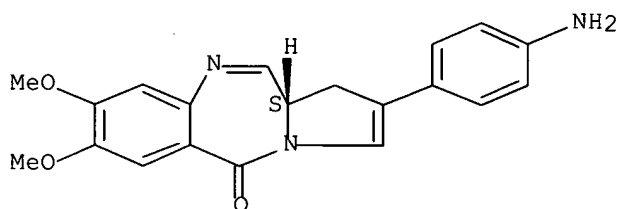
Absolute stereochemistry.



RN 864754-95-0 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 2-(4-aminophenyl)-1,11a-dihydro-7,8-dimethoxy-, (11aS)- (9CI) (CA INDEX NAME)

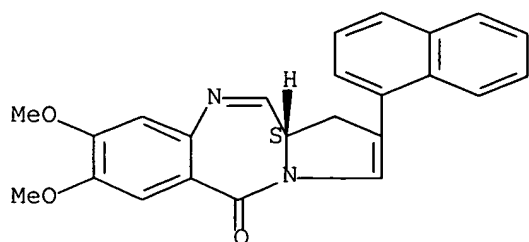
Absolute stereochemistry.



RN 864754-96-1 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,11a-dihydro-7,8-dimethoxy-2-(1-naphthalenyl)-, (11aS)- (9CI) (CA INDEX NAME)

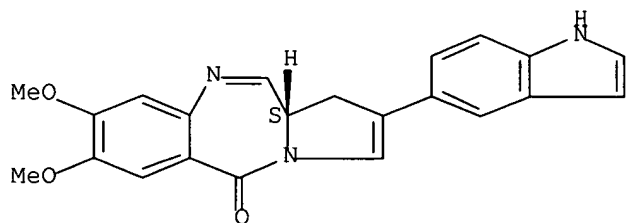
Absolute stereochemistry.



RN 864754-97-2 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,11a-dihydro-2-(1H-indol-5-yl)-7,8-dimethoxy-, (11aS)- (9CI) (CA INDEX NAME)

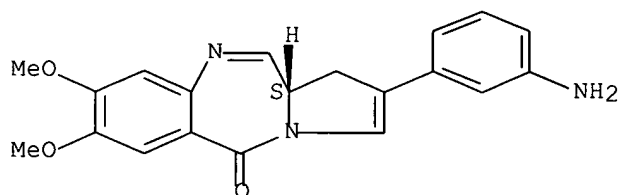
Absolute stereochemistry.



RN 864754-98-3 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 2-(3-aminophenyl)-1,11a-dihydro-7,8-dimethoxy-, (11aS)- (9CI) (CA INDEX NAME)

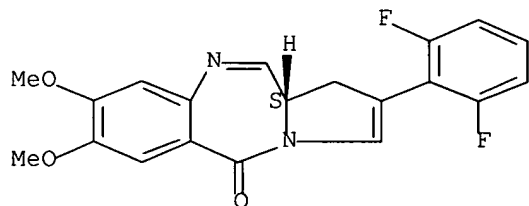
Absolute stereochemistry.



RN 864754-99-4 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 2-(2,6-difluorophenyl)-1,11a-dihydro-7,8-dimethoxy-, (11aS)- (9CI) (CA INDEX NAME)

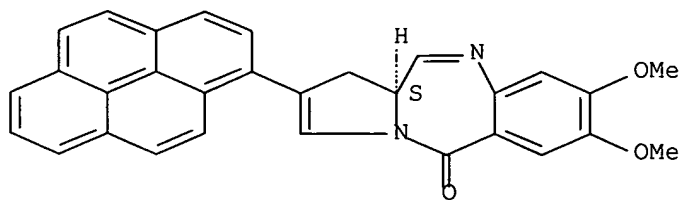
Absolute stereochemistry.



RN 864755-00-0 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,11a-dihydro-7,8-dimethoxy-2-(1-pyrenyl)-, (11aS)- (9CI) (CA INDEX NAME)

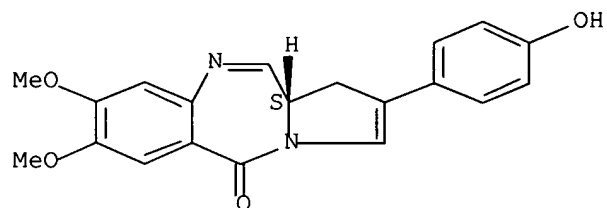
Absolute stereochemistry.



RN 864755-01-1 CAPLUS

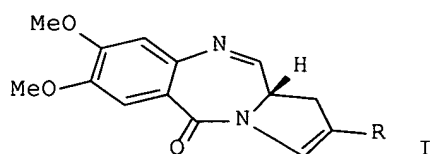
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,11a-dihydro-2-(4-hydroxyphenyl)-7,8-dimethoxy-, (11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



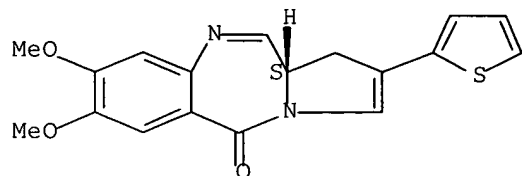
RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN
 AN 2004:767272 CAPLUS Full-text
 DN 141:410907
 TI Application of the Stille coupling reaction to the synthesis of
 C2-substituted endo-exo unsaturated pyrrolo[2,1-c][1,4]benzodiazepines
 (PBDs)
 AU Tiberghien, Arnaud C.; Hagan, David; Howard, Philip W.; Thurston, David E.
 CS Cancer Research UK Gene Targeted Drug Design Research Group, Department of
 Pharmaceutical and Biological Chemistry, The School of Pharmacy, London,
 WC1N 1AX, UK
 SO Bioorganic & Medicinal Chemistry Letters (2004), 14(20), 5041-5044
 CODEN: BMCLE8; ISSN: 0960-894X
 PB Elsevier B.V.
 DT Journal
 LA English
 OS CASREACT 141:410907
 GI



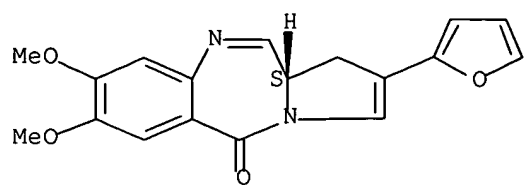
AB The Stille coupling reaction has been used to introduce novel vinyl, alkynyl,
 and heterocyclic substituents to the C2-position of pyrrolo[2,1-
 c][1,4]benzodiazepine dilactams. Sodium borohydride reduction followed by
 N10-SEM deprotection has provided five analogs I (R = H, CH₂:CH, 2-thienyl,
 C.tplbond.CPh, 2-furyl) that contain C2-endo/exo-unsatn. and novel C2-
 substituents. These analogs have significant multilog cytotoxicity profiles
 in the NCI 60-Cell Line screen, and provide new SAR data for the PBD family.
 IT 692760-82-OP 692760-84-2P
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL
 (Biological study); PREP (Preparation)
 (preparation of C2-substituted endo-exo unsatd. pyrrolo[2,1-
 c][1,4]benzodiazepines via Stille coupling reaction and subsequent
 reduction/deprotection)
 RN 692760-82-0 CAPLUS
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,11a-dihydro-7,8-dimethoxy-2-
 (2-thienyl)-, (11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 692760-84-2 CAPLUS
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 2-(2-furanyl)-1,11a-dihydro-7,8-
 dimethoxy-, (11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

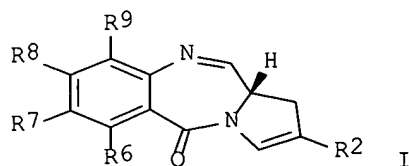


RE.CNT 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

App's

L5 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN
 AN 2004:430806 CAPLUS Full-text
 DN 140:423715
 TI Preparation of pyrrolobenzodiazepines as anticancer agents agents
 IN Thurston, David Edwin; Howard, Philip Wilson
 PA Spirogen Limited, UK
 SO PCT Int. Appl., 74 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004043963	A1	20040527	WO 2003-GB4963	20031114
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
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	CA 2505489	AA	20040527	CA 2003-2505489	20031114
	AU 2003282251	A1	20040603	AU 2003-282251	20031114
	EP 1575955	A1	20050921	EP 2003-773870	20031114
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
	BR 2003016241	A	20051004	BR 2003-16241	20031114
	CN 1735616	A	20060215	CN 2003-80108373	20031114
	JP 2006507313	T2	20060302	JP 2004-550845	20031114
	US 2006128693	A1	20060615	US 2005-534825	20051020
PRAI	GB 2002-26593	A	20021114		
	WO 2003-GB4963	W	20031114		
OS	MARPAT 140:423715				
GI					



AB The title compds. (I), salts, solvates, chemical protected forms, and prodrugs thereof, [R6-R9 = H, R, OH, OR, SH, SR, NH2, NHR, NHRR', nitro, Me3Sn, halo (where R, R' = optionally substituted C1-7 alkyl, C3-20 heterocyclyl, or C5-20 aryl); or the compound is a dimer with each monomer being of formula I, where the R8 groups of each monomers form together a dimer bridge having the formula -X-R''-X- linking the monomers (where R'' = C3-12 alkylene, which chain may be interrupted by one or more heteroatoms, e.g. O, S, NH, and/or aromatic rings, e.g. benzene or pyridine, and each X = O, S, or NH); or any pair of adjacent groups from R6 to R9 together form a group -O-(CH2)p-O- (where p = 1, 2); R2 = (i) optionally substituted naphthyl, (ii) optionally substituted thiophenyl or furanyl, or (iii) Ph substituted by: (a) one or more Cl or F, (b) Et or n-Pr, (c) 4-tert-Bu, or (d) 2-Me; or (e) two Me groups in the 2- and 6-positions] are prepared Also disclosed are (1) the use of the compound I in the manufacture of a medicament for treating a proliferative disease and (2) a method of treatment of a proliferative disease, comprising administering to a

subject in need of treatment a therapeutically-effective amount of the compound I. Thus, (11aS)-5,10,11,11a-tetrahydro-7,8-dimethoxy-10-[2-(trimethylsilyl)ethoxymethyl]-2-[[[(trifluoromethyl)sulfonyl]oxy]-5,11-dioxo-1H-pyrrolo[2,1-c][1,4]benzodiazepine was coupled with 4-ethylbenzeneboronic acid in the presence of tetrakis(triphenylphosphine)palladium(0) and Na₂CO₃ in a mixture of EtOH, H₂O, and benzene at room temperature for 41 h to give I (R₆ = R₉ = H, R₆ = R₇ = OMe, R₂ = 4-ethylphenyl) (II). II showed IC₅₀ of <0.1 µg/mL for inhibiting the proliferation of breast MACL MCF7, renal RXF 955L, and melanoma MEXF 462NL cancer cells.

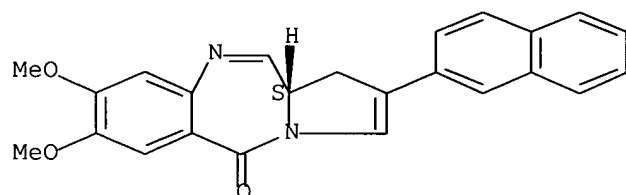
IT 692760-70-6P, (11aS)-1,11a-Dihydro-7,8-dimethoxy-2-(2-naphthyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one 692760-72-8P, (11aS)-1,11a-Dihydro-7,8-dimethoxy-2-(4-tert-butylphenyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one 692760-74-0P, (11aS)-1,11a-Dihydro-7,8-dimethoxy-2-(4-chlorophenyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one 692760-76-2P, (11aS)-1,11a-Dihydro-7,8-dimethoxy-2-(4-fluorophenyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one 692760-78-4P, (11aS)-1,11a-Dihydro-7,8-dimethoxy-2-(2-methylphenyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one 692760-80-8P, (11aS)-1,11a-Dihydro-7,8-dimethoxy-2-(4-ethylphenyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one 692760-82-0P, (11aS)-1,11a-Dihydro-7,8-dimethoxy-2-(thiophen-2-yl)-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one 692760-84-2P, (11aS)-1,11a-Dihydro-7,8-dimethoxy-2-(2-furyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one 692760-86-4P, (11aS)-1,11a-Dihydro-7,8-dimethoxy-2-(2,6-dimethylphenyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of pyrrolobenzodiazepines as anticancer agents)

RN 692760-70-6 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,11a-dihydro-7,8-dimethoxy-2-(2-naphthalenyl)-, (11aS)- (9CI) (CA INDEX NAME)

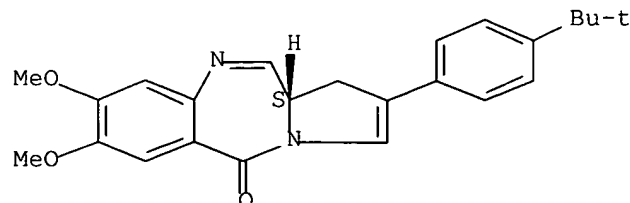
Absolute stereochemistry.



RN 692760-72-8 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 2-[4-(1,1-dimethylethyl)phenyl]-1,11a-dihydro-7,8-dimethoxy-, (11aS)- (9CI) (CA INDEX NAME)

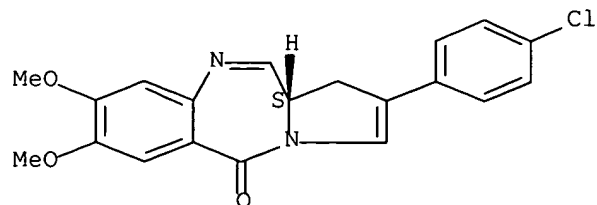
Absolute stereochemistry.



RN 692760-74-0 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 2-(4-chlorophenyl)-1,11a-dihydro-7,8-dimethoxy-, (11aS)- (9CI) (CA INDEX NAME)

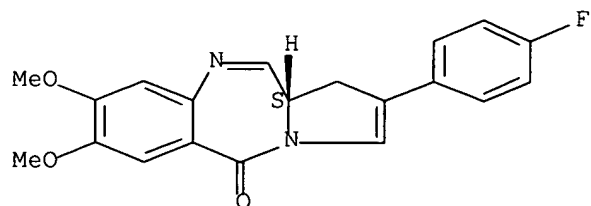
Absolute stereochemistry.



RN 692760-76-2 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 2-(4-fluorophenyl)-1,11a-dihydro-7,8-dimethoxy-, (11aS)- (9CI) (CA INDEX NAME)

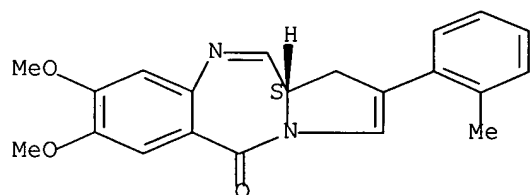
Absolute stereochemistry.



RN 692760-78-4 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,11a-dihydro-7,8-dimethoxy-2-(2-methylphenyl)-, (11aS)- (9CI) (CA INDEX NAME)

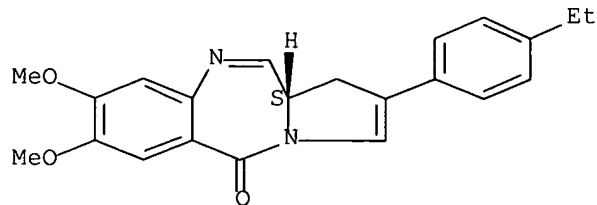
Absolute stereochemistry.



RN 692760-80-8 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 2-(4-ethylphenyl)-1,11a-dihydro-7,8-dimethoxy-, (11aS)- (9CI) (CA INDEX NAME)

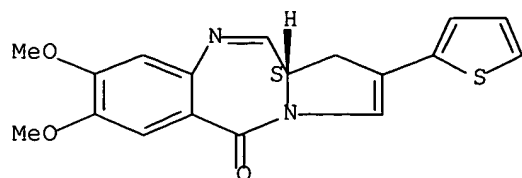
Absolute stereochemistry.



RN 692760-82-0 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,11a-dihydro-7,8-dimethoxy-2-(2-thienyl)-, (11aS)- (9CI) (CA INDEX NAME)

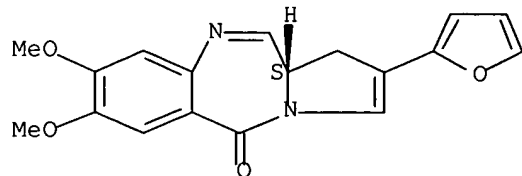
Absolute stereochemistry.



RN 692760-84-2 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 2-(2-furanyl)-1,11a-dihydro-7,8-dimethoxy-, (11aS)- (9CI) (CA INDEX NAME)

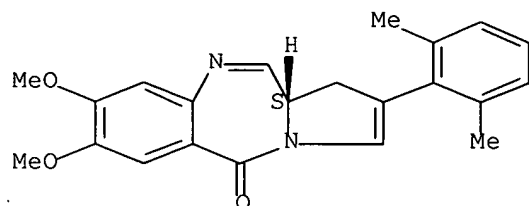
Absolute stereochemistry. Rotation (+).



RN 692760-86-4 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 2-(2,6-dimethylphenyl)-1,11a-dihydro-7,8-dimethoxy-, (11aS)- (9CI) (CA INDEX NAME)

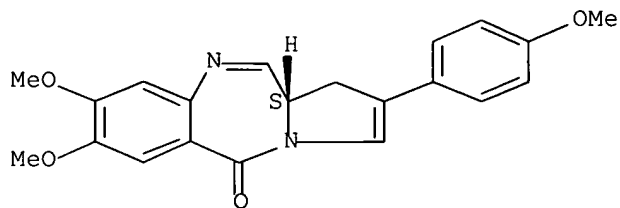
Absolute stereochemistry.



RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

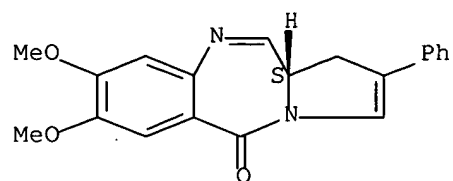
L5 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN
 AN 2002:557716 CAPLUS Full-text
 DN 138:122628
 TI Synthesis of novel C2-aryl pyrrolobenzodiazepines (PBDs) as potential antitumor agents
 AU Cooper, Nectaroula; Hagan, David R.; Tiberghien, Arnaud; Ademefun, Temitope; Matthews, Charles S.; Howard, Philip W.; Thurston, David E.
 CS CRUK Gene Targeted Drug Design Research Group, School of Pharmacy, University of London, London, WC1N 1AX, UK
 SO Chemical Communications (Cambridge, United Kingdom) (2002), (16), 1764-1765
 CODEN: CHCOFS; ISSN: 1359-7345
 PB Royal Society of Chemistry
 DT Journal
 LA English
 OS CASREACT 138:122628
 AB Three novel C2-aryl substituted pyrrolobenzodiazepines (PBDs) have been synthesized and evaluated in a number of cell lines revealing selective cytotoxicity at the sub-nanomolar level towards melanoma and ovarian cancer cell lines. Compds. thus prepared included (11aS)-1,11a-dihydro-7,8-dimethoxy-2-phenyl-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one, (11aS)-1,11a-dihydro-7,8-dimethoxy-2-(4-methylphenyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one and (11aS)-1,11a-dihydro-7,8-dimethoxy-2-(4-methoxyphenyl)-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one. (11AS)-1,2,3,11a-tetrahydro-7,8-dimethoxy-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one was also screened against cancer cell lines.
 IT 260544-29-4P, (11aS)-1,11a-Dihydro-7,8-dimethoxy-2-(4-methoxyphenyl)-5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one
 260544-30-7P, (11aS)-1,11a-Dihydro-7,8-dimethoxy-2-phenyl-5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one 489475-06-1P, (11aS)-1,11a-Dihydro-7,8-dimethoxy-2-(4-methylphenyl)-5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
 (preparation of C2-aryl pyrrolobenzodiazepines as potential antitumor agents)
 RN 260544-29-4 CAPLUS
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,11a-dihydro-7,8-dimethoxy-2-(4-methoxyphenyl)-, (11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 260544-30-7 CAPLUS
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,11a-dihydro-7,8-dimethoxy-2-phenyl-, (11aS)- (9CI) (CA INDEX NAME)

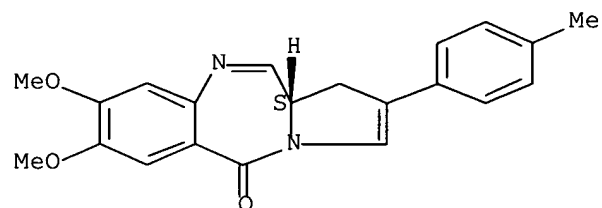
Absolute stereochemistry.



RN 489475-06-1 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,11a-dihydro-7,8-dimethoxy-2-(4-methylphenyl)-, (11aS)- (9CI) (CA INDEX NAME)

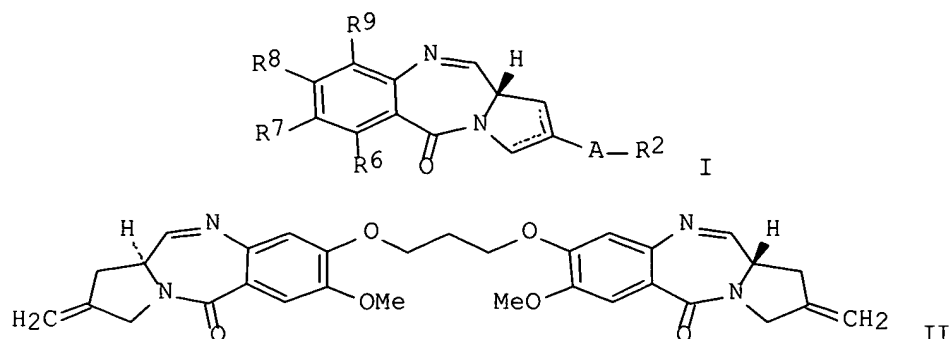
Absolute stereochemistry.



RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN
 AN 2000:161284 CAPLUS Full-text
 DN 132:207851
 TI Preparation of pyrrolobenzodiazepines (PBDs) as antitumor agents
 IN Thurston, David Edwin; Howard, Philip Wilson
 PA The University of Portsmouth Higher Education Corporation, UK
 SO PCT Int. Appl., 258 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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	PT 1193270	T	20031031	PT 2001-129700	19990827
	NZ 510493	A	20031128	NZ 1999-510493	19990827
	ES 2199200	T3	20040216	ES 2001-129700	19990827
	EP 1413582	A1	20040428	EP 2003-28817	19990827
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	ES 2244210	T3	20051201	ES 1999-943066	19990827
	AT 320436	E	20060415	AT 2003-28817	19990827
	US 7049311	B1	20060523	US 2001-763767	20010226
	US 2003120069	A1	20030626	US 2001-21213	20011212
	US 7067511	B2	20060627		
	US 2006148788	A1	20060706	US 2006-367241	20060302
PRAI	GB 1998-18733	A	19980827		
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OS	MARPAT 132:207851				
GI					



AB 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one derivs. (I) [wherein A = CH₂ or a single bond; R = (un)substituted (ar)alkyl, (ar)alkenyl, or (ar)alkynyl; R₂ = R, OH, OR, CO₂H, CO₂R, COH, COR, SO₂R, CN; R₆, R₇, R₈, and R₉ = independently H, R, OH, OR, halo, NH₂, NHR, NO₂, SnMe₃; or the compound is a dimer with each monomer being the same or different and being of formula I and the R₈ groups of the monomers form a -X-R'-X- bridge, where R' is an alkylene chain which may contain ≥ 1 heteroatoms and/or aromatic rings and/or carbon-carbon double or triple bonds, and each X = independently O, S, or N] were prepared for the treatment of gene-based diseases, e.g. neoplastic diseases and Alzheimer's disease, and also bacterial, parasitic, and viral infections. For example, II was synthesized in a 6-step sequence. 1',3'-Bis(4-carboxy-2-methoxy-5-nitrophenoxy)propane (preparation given) was bisamidated with (2S)-2-(tert-butyltrimethylsilyloxymethyl)-4-methylenepyrrolidine (74%). TBAF-mediated cleavage of the silyl protecting groups (94%), followed by reduction of the nitro groups by NH₂NH₂ in the presence of Raney Ni (63%) and N-acylation with allyl chloroformate (50%), gave the protected diamine. Ring closure was accomplished under Swern oxidation conditions, (COCl)₂-DMSO and TEA, (32%). Finally, the imine was formed from the carbinolamine by N-deprotection using Pd(PPh₃)₄ and elimination of H₂O (77%). Both large scale in vitro cytotoxicity cell screens and in vivo hollow fiber and human tumor xenograft assays were performed on selected compds. of the invention. For instance, II exhibited potent and selective cytotoxicity against the lung cancer cell line NCI-H460, the colon cell line HCC-2998, the CNS cancer cell line SNB-75, and the melanoma cell lines MALME-3M (very potent, 0.08 μM) and UACC-62 (very potent, 0.07 μM). In human xenograft studies against five types of tumors, II demonstrated anticancer activity with mixed toxicity results. In addition, II was shown to be the most potent DNA-stabilizing agent known to date according to a DNA helix melting temperature assay. The IC₅₀ value for II in the A2780 human ovarian carcinoma cell line was only 23 pM, a 320-fold increase in cytotoxicity compared to the known antitumor agent DSB-120 (IC₅₀ = 5.2 nM). Remarkably, II was also almost 9000-fold more potent in the cisplatin-resistant A2780cisR cell line (IC₅₀ = 24 pM) than DSB-120 (IC₅₀ = 0.21 mM), suggesting that II may have potential in the treatment of cisplatin-refractory disease.

IT 260544-29-4P, UP 2092 260544-30-7P, UP 2095

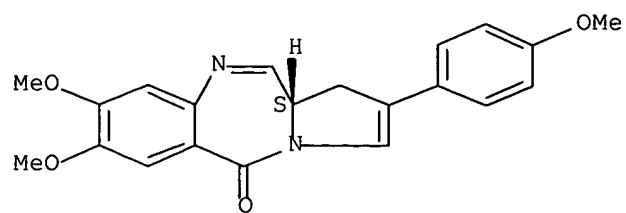
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(target compound; preparation of 5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one antitumor agents from 2-amino- or 2-nitrobenzoic acid derivs. and pyrrolidines)

RN 260544-29-4 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,11a-dihydro-7,8-dimethoxy-2-(4-methoxyphenyl)-, (11aS)- (9CI) (CA INDEX NAME)

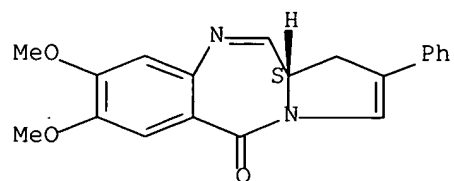
Absolute stereochemistry.



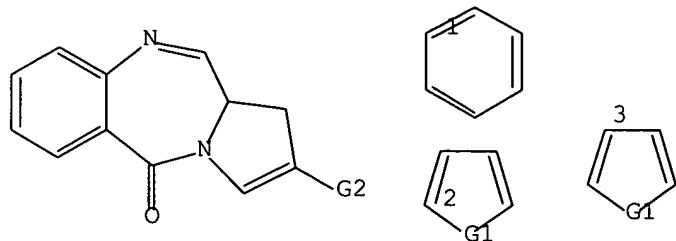
RN 260544-30-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 1,11a-dihydro-7,8-dimethoxy-2-phenyl-, (11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



=> d l2; d his; log y
 L2 HAS NO ANSWERS
 L1 STR



G1 O,S
 G2 [01], [02], [03]

Structure attributes must be viewed using STN Express query preparation.
 L2 QUE ABB=ON PLU=ON L1

(FILE 'HOME' ENTERED AT 20:12:09 ON 31 AUG 2006)

FILE 'REGISTRY' ENTERED AT 20:12:22 ON 31 AUG 2006

L1 STRUCTURE UPLOADED
 L2 QUE L1
 L3 2 S L2
 L4 35 S L2 FUL

FILE 'CAPLUS' ENTERED AT 20:12:51 ON 31 AUG 2006

L5 5 S L4

COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	26.01	193.16
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL
	ENTRY	SESSION
CA SUBSCRIBER PRICE	-3.75	-3.75

STN INTERNATIONAL LOGOFF AT 20:13:34 ON 31 AUG 2006